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SOME REMARKS ON THE MOVEMENT OF CHROMOSOMES DURING CELL DIVISION

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THE UNIVERSITY OF CHICAGO

The possibility of drawing conclusions about the nature of the forces acting upon the chromosomes during division from observation of the rates of their movement in anaphase is pointed out. Some available data are discussed, and shown to agree quantitatively with the assumption that during anaphase the chromosomes are pulled apart by contracting elastic fibers.

In a previous outline of a physicomathematical theory of mitosis (Rashevsky, 1938; chapter xiii) it has been suggested that the chromosomes are kept in a stable position in the equatorial plate during metaphase by repulsion diffusion forces from two "equivalent" diffusion centers at the poles of the spindle. During anaphase they become connected by elastic fibers with the poles. When the elastic forces exceed both the diffusion forces as well as the forces that may hold together the daughter chromosomes, these are pulled by contracting fibers towards the poles.

Since the chromosomes move in a viscous medium and their velocities are small, the inertial terms in the equations of their motion may be neglected and we may set their velocity at any moment as proportional to the force acting at this moment and inversely proportional to the viscosity. Denoting by y the distance of a chromosome from the pole, the elastic force pulling it towards the pole will be approximately proportional to y , while the diffusion force, repelling it would be approximately proportional to $1/y^2$. The equation of motion of a chromosome will be of the form:

$$\frac{dy}{dt} = -ay + \frac{b}{y^2}, \quad (1)$$

a and b being constants. Integrating equation (1) and denoting by y_0 the value of y for $t = 0$, we find:

$$\log \frac{ay^3 - b}{ay_0^3 - b} = -3at. \quad (2)$$

For very small values of b , or very large values of y , equation (2) reduces to

$$\log y = -at + \text{Const.} \quad (3)$$

In the presence of only elastic forces a straight line relationship would hold between $\log y$ and t . In the presence of repelling forces also, the more complex equation (2) will hold.

Data that can be used to verify one of the two above equations have been supplied by H. N. Barber (1939), who gives relative distances of chromosomes during anaphase for various cells. Unfortunately, not all of his data can be used for the present purpose. The three sets of curves for *Tradescantia* do obviously not satisfy the simple conditions considered here. In those cases the chromosomes after reaching a maximum separation move again towards each other. This peculiarity seems to be characteristic of the *Tradescantia* cells, so far as Barber's data go. It may be due to the presence of relatively rigid cell walls, which make the dynamics of the cell division different from that of a freely elongating cell. On animal cells there are four sets of data: two on the first meiosis in the spermatocytes of *Stenobothrus*, for two different chromosomes in the same cell, and two on the second meiosis, for two sister cells. In the first two cases the situation is again complicated by the presence of chiasmata. Thus only the last two sets seem to fulfill the simple conditions assumed above.

As seen from Figure 1, both sets of data are represented within the limits of experimental error by the simple equation (2). There

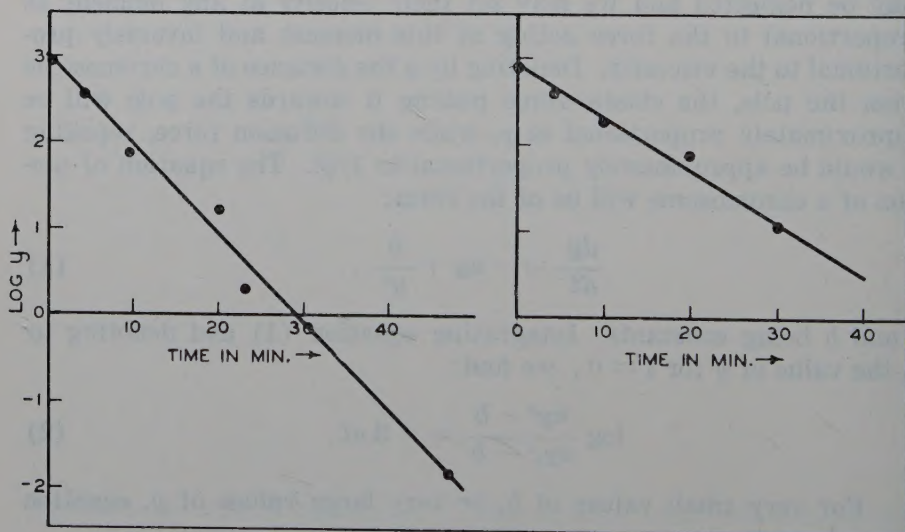


FIGURE 1

seems thus to be no indication in this case of the presence of any repelling forces.

This immediately raises the question on the nature of mechanical stability of the equatorial plate. Quite regardless of the nature and mechanism of the forces present, the chromosomes will be located stably in the equatorial plane only under one of the two conditions: either they are attracted to the poles by forces *which increase with distance*, or else they are repelled by the poles by forces *which decrease with distance*.

The only known forces, that increase with distance are the elastic forces. Thus we seem to be led to the conclusion that the elastic spindle fibers are not only responsible for the movement of the chromosomes at anaphase, but also for their arrangement in the equatorial plane at metaphase, unless we assume that some forces are present during prophase and metaphase, which disappear at the beginning of anaphase.

In any case these considerations support *quantitatively* the theory that the movement of chromosomes during anaphase is due to an elastic pull by contracting spindle fibers.

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ON REINFORCEMENT AND INTERFERENCE BETWEEN STIMULI

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It is shown that the current "two-factor" theory of nerve excitation can account for sustained inhibition or enhancement by a sequence of stimulus pulses, and for the decrease in the reinforcement period with each successive pulse of the train.

1. *Excitation equations.* The basic equations in Rashevsky's excitation theory are*

$$\begin{aligned}\frac{d\varepsilon}{dt} &= KI - k\varepsilon, \\ \frac{dj}{dt} &= MI - mj,\end{aligned}\tag{1}$$

which describe the variation of a quantity $\sigma = \varepsilon - j$ under the influence of a stimulating current $I(t)$ reckoned as positive at the cathode and negative at the anode of the stimulating electrodes. The equations are considered to hold so long as σ remains below a positive threshold value h . When σ becomes equal to h , excitation occurs, and the theory makes no claim to hold during the succeeding cycle of membrane activity. It is valid again by the time the nerve has returned to its resting state, and presumably somewhat earlier than this, such as near the beginning of the relative refractory period.

The solution of the equations (1) is given by

$$\begin{aligned}\varepsilon(t) &= e^{-kt} [\varepsilon_0 + K \int_0^t I(x) e^{kx} dx] ; \\ j(t) &= e^{-mt} [j_0 + M \int_0^t I(x) e^{mx} dx] ;\end{aligned}\tag{2}$$

*Here ε and j take the place of $\varepsilon - \varepsilon_0$ and $j - j_0$ in one of Rashevsky's notations (1940, p. 108), and are not restricted to positive values. Our threshold h corresponds to his quantity $j_0 - \varepsilon_0$. The present notation is that used by him in another place. (1940, p. 123).

where the zero subscripts denote values at $t = 0$.†

Equivalent formulations of the theory have been given by Hill and by Monnier, but for our present purposes the Rashevsky form (1) is the most convenient.

For application to actual nerves it is appropriate to restrict attention to the case

$$\begin{aligned} K &> M > 0, \\ k &> m > 0, \end{aligned} \quad (3)$$

and without loss of generality we may set

$$h = 1. \quad (4)$$

2. *No stimulus.* Starting from an initial state of the nerve specified by values ε_0 and j_0 it is seen that in the absence of stimulation, σ varies according to

$$\sigma = \varepsilon_0 e^{-kt} - j_0 e^{-mt}. \quad (5)$$

Depending upon the values ε_0 and j_0 there are various possibilities for the time course of σ . In any case both σ and $d\sigma/dt$ vanish at $t = \infty$; in the various cases they each have 0 or 1 finite positive roots. The zero value of σ comes at the time

$$t_0 = \frac{1}{k-m} \log \frac{\varepsilon_0}{j_0}, \quad (6)$$

provided that this quantity is real and positive; while a maximum or a minimum occurs at

$$t_m = \frac{1}{k-m} \log \frac{k\varepsilon_0}{mj_0}, \quad (7)$$

if this is real and positive. Since $k > m$ it is seen that t_m exists if t_0 does, and that $t_m > t_0$. There are three cases as illustrated in Figure 1, and occurring as follows:

- (a) $\frac{\varepsilon_0}{j_0} > 1$; both t_0 and t_m exist.
- (b) $1 > \frac{\varepsilon_0}{j_0} > \frac{m}{k}$; t_m exists, but not t_0 .
- (c) $\frac{\varepsilon_0}{j_0} < \frac{m}{k}$; neither t_m nor t_0 exist.

Inspection of the diagrams shows that the only cases in which

† Rashevsky's ε_0 and j_0 (1940, p. 108) have a different meaning.

σ rises to a positive value greater than σ_0 are in (a) with σ_0 negative and in (b) with σ_0 positive. Upon reference to (8) it is found that for one or the other of these cases to exist, it is necessary and sufficient that the three inequalities

$$\begin{aligned}\varepsilon &< 0 \\ j &< 0 \\ k\varepsilon - mj &< 0\end{aligned}\tag{9}$$

shall all be initially satisfied. Hence *excitation cannot occur in the absence of a stimulus unless previous stimulation has brought the nerve to a state in which (9) holds*. Condition (9) is necessary but not sufficient for spontaneous excitation to occur. An example of excitation occurring in the absence of a stimulus is at the anode after a sufficiently strong current has been broken.

If a nerve free of stimulation does not satisfy (9) at one moment, then it never will at any later moment. On the other hand a free nerve can satisfy (9) only up to the time t_m , since the quantity on the left of the last inequality is simply $-d\sigma/dt$ and so changes sign at t_m .

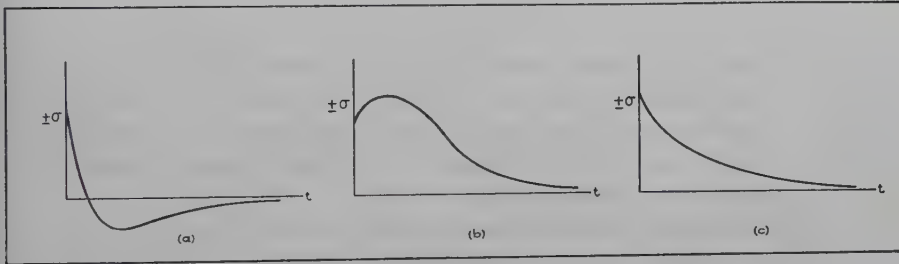


FIGURE 1

From (2) it is seen that a positive stimulus ($I > 0$) applied to a resting nerve ($\varepsilon_0 = j_0 = 0$) can never bring the nerve into a state in which (9) holds, and thus *excitation cannot occur after the cessation of a positive stimulus applied to a resting nerve*.

3. *Instantaneous pulse*. For t very small the exponential factors in (2) are sensibly equal to unity and thus after a very brief or instantaneous pulse we have

$$\begin{aligned}\varepsilon &= \varepsilon_0 + KQ \\ j &= j_0 + MQ ;\end{aligned}\tag{10}$$

where
$$Q = \int_0^t I(x) dx \tag{11}$$

is the total quantity of electricity passed during the pulse. Upon reference to (3) it is seen that a positive or cathodic (i.e. $Q > 0$) pulse increases all three quantities on the left sides of the inequalities (9). Hence *a nerve which is about to fire spontaneously can be stopped from so doing by a sufficiently strong positive pulse. A positive pulse cannot leave a nerve in state (9) unless it was already there.*

From (10) it follows at once that

$$\sigma = \sigma_0 + (K - M)Q. \quad (12)$$

Let Q_0 denote the positive pulse strength just sufficient to fire the resting nerve. Then upon setting $\sigma = h = 1$, $\sigma_0 = 0$, it is seen that

$$K - M = \frac{1}{Q_0}. \quad (13)$$

If Q is the positive pulse just sufficient to produce *immediate* excitation of the nerve in some other state,* then the value of σ in that state just before the pulse passed was

$$\sigma = 1 - \frac{Q}{Q_0}. \quad (14)$$

Thus the value of σ can be experimentally determined (Hill, 1936; Coppee, 1936; Katz and Schmitt, 1940), providing a test for the theory. Apart from the constant unity, σ is merely the negative of the "relative threshold" and may thus be called the "excitability". Its range is from $-\infty$, corresponding to absolute refractoriness, up to unity, at which excitation occurs.

4. *Sequence of instantaneous pulses.* After a positive pulse of strength Q is applied to a resting nerve, σ is given by (5) with

$$\begin{aligned} \varepsilon_0 &= KQ \\ j_0 &= MQ. \end{aligned} \quad (15)$$

Since $K > M$, we have case (a) in (8) and in Figure 1 (cf. Hill, 1936, Figure 76). A second positive pulse following the first within an interval up to t_0 will be reinforced, while if it comes later than t_0 , it will be opposed by the stimulus trace or residue of the first. For any two sub-liminal pulses such that $Q_1 + Q_2 > Q_0$ there will be a period, greater than zero and less than t_0 , within which they will "sum" to bring about excitation. This interval depends on the nerve and on

* The word *immediate* is needed to handle those cases in which the nerve was about to fire spontaneously. A zero pulse would then be followed by excitation, but not immediately.

the strengths of the stimuli. Furthermore, if the strengths are unequal it depends on the order in which they are presented, being greater if the weaker stimulus is presented first.

At a time Δ after the first pulse, we have

$$\begin{aligned}\varepsilon &= KQe^{-k\Delta} \\ j &= MQe^{-m\Delta} ;\end{aligned}\tag{16}$$

and if another equal pulse be then applied these values jump to

$$\varepsilon = KQ(1 + e^{-k\Delta})\tag{17}$$

$$j = MQ(1 + e^{-m\Delta}).\tag{18}$$

Continuing in this manner with equal and equally spaced stimuli we have just after the n -th pulse

$$\varepsilon = KQ(1 + e^{-k\Delta} + e^{-2k\Delta} + \dots + e^{-(n-1)k\Delta}),\tag{19}$$

with a similar expression for j . Upon summing the geometric progressions we obtain

$$\begin{aligned}\varepsilon &= KQ \frac{1 - e^{-nk\Delta}}{1 - e^{-k\Delta}} \\ j &= MQ \frac{1 - e^{-nm\Delta}}{1 - e^{-m\Delta}},\end{aligned}\tag{20}$$

which, as n becomes large, reduce to

$$\begin{aligned}\varepsilon &= KQ \frac{1}{1 - e^{-k\Delta}} \\ j &= MQ \frac{1}{1 - e^{-m\Delta}}.\end{aligned}\tag{21}$$

It is seen from (20) that ε and j are always positive. Hence (9) is never satisfied and excitation cannot occur between pulses. Also, if σ is less than zero just after a pulse it remains so until the next pulse, as may be seen by noting that case (a) in (8) is not possible with $j_0 > \varepsilon_0 > 0$. Consider in particular the steady state for which (21) holds. σ will be less than zero at the beginning of a cycle (just after a pulse) if and only if the quantity

$$\frac{K}{M} \frac{1 - e^{-m\Delta}}{1 - e^{-k\Delta}}\tag{22}$$

is less than unity. The second factor has its minimum value m/k at $\Delta = 0$ and increases monotonically to unity as Δ becomes large. Hence if

$$\frac{K}{k} < \frac{M}{m} \quad (23)$$

the quantity σ can be maintained less than zero throughout the steady state cycle if Δ is small enough.

Conversely, if σ is greater than zero at the end of a cycle it must have been so throughout. In the steady state the values at the end of a cycle (just before a pulse) are

$$\begin{aligned} \varepsilon &= KQ \frac{e^{-k\Delta}}{1 - e^{-k\Delta}} = KQ \frac{1}{e^{k\Delta} - 1} \\ j &= MQ \frac{e^{-m\Delta}}{1 - e^{-m\Delta}} = MQ \frac{1}{e^{m\Delta} - 1}. \end{aligned} \quad (24)$$

Hence σ will be greater than zero throughout the cycle if and only if the quantity

$$\frac{K}{M} \frac{e^{m\Delta} - 1}{e^{k\Delta} - 1} \quad (25)$$

is greater than unity. The second factor has its maximum value m/k at $\Delta = 0$ and decreases monotonically to zero as Δ becomes large. Hence if

$$\frac{K}{k} > \frac{M}{m} \quad (26)$$

the quantity σ can be maintained greater than zero throughout the steady state cycle if Δ is small enough.

In either case, (23) or (26), if Δ is not sufficiently small then $\sigma > 0$ during the first part of the cycle and $\sigma < 0$ during the remainder of the cycle. The mean value of σ over a cycle gives a measure of the average increase in excitability. Defining

$$\Delta \bar{\sigma} = \int_0^{\Delta} \sigma dt, \quad (27)$$

we find from (5) and (21) that in the steady state

$$\bar{\sigma} = \frac{Q}{\Delta} \left(\frac{K}{k} - \frac{M}{m} \right). \quad (28)$$

From (1) it is seen that this state is the steady state value of σ which would be produced by a constant current of strength $I = Q/\Delta$, and is

thus somewhat of the nature of an electrotonus effect. The relation of (28) to (23) and (26) is obvious, and sheds additional light upon the significance of a "normal accommodation" (Hill, 1936; Rashevsky, 1940, p. 111) described by $K/k = M/m$.

From (6) and (20) it is seen that the "reinforcement period" after the n -th pulse is proportional to the logarithm of

$$\frac{K}{M} \frac{1 - e^{-m\Delta}}{1 - e^{-k\Delta}} \frac{1 - e^{-nk\Delta}}{1 - e^{-nm\Delta}}. \quad (29)$$

The last factor decreases monotonically to unity as n increases, and so *the reinforcement period diminishes with each successive pulse*. (Lorentz de No, 1938, p. 240). Since $K > M$ the reinforcement period is always positive after the first pulse ($n=1$), and is in fact equal to the time at which σ reaches its maximum value when a steady current is applied to the resting nerve. If, however, the product of the first two factors in (29) is less than unity, then the reinforcement period becomes negative after a sufficient number of pulses and the nerve is inhibited from then on as long as the stimuli continue, in accordance with the discussion of (22).

Let $\sigma(n)$ be the value of σ immediately after the n -th pulse, and denote

$$\delta(n) = \sigma(n+1) - \sigma(n). \quad (30)$$

If the first n pulses have failed to fire the nerve, then there is a possibility of the next pulse being successful only if $\delta(n) > 0$. From (19) it is seen that

$$\delta(n) = Q(K e^{-nk\Delta} - M e^{-nm\Delta}), \quad (31)$$

so that δ is negative for n sufficiently large. If $\delta(1) < 0$ then so is δ for all larger values of n , and $\sigma(n)$ is a monotonically decreasing function of n . If $\delta(1) > 0$ (which, upon reference to (6) and (29), is the same as saying that Δ is less than the reinforcement period after the first stimulus) then $\sigma(n)$ first rises and then falls as n increases, attaining its maximum value at one (or possibly both) of the two pulses occurring respectively just before and just after the time

$$\frac{1}{k-m} \log \frac{K}{M}. \quad (32)$$

This time is the reinforcement period for a single pulse and also, as mentioned above, the time for the attainment of a maximum σ under the influence of a constant current. The rise and fall of σ under a steady current is thus quite closely related to the rise and fall of its peak values with a steady sequence of pulses.

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STUDIES IN THE MATHEMATICAL BIOPHYSICS OF DISCRIMINATION AND CONDITIONING I

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A mechanism with properties of discrimination and conditioning is discussed mathematically with reference to special cases in the problem of error elimination: elimination of the longer of two paths to a goal, elimination of a blind as well as a return alley, and Lashley's jumping problem. For each case equations are derived which are qualitatively correct as far as was determined. Several qualitative deductions are made and these are substantiated by data available. In principle, the theory makes it possible to predict, for any trial, the number of errors at any junction of a maze provided certain experimental conditions are satisfied, and if a sufficient number of experimental values are given to determine the parameters of the system.

A theory of error elimination based on a neural mechanism has been discussed in previous papers (Rashevsky, 1936, Landahl, 1938b). We shall continue the theoretical development by discussing results from modified assumptions about the mechanism and its functions, and by giving approximate solutions to several specific experimental situations.

1. *General theoretical formulation.* The basis for the following development is the neural mechanism of Figure 1, in which the fibers have the properties postulated by N. Rashevsky (1938, chap. xxii). The stimulus S_c presented alone produces the response R_c which, because of the nature of the experiment necessarily results in another response R_1 . For example, a rat responds to the sensory cues of an alley entrance by entering the alley, and this act leads to some further response such as that of eating. The response R_1 and the stimulus S_c may then become conditioned with successive repetitions. Similarly, if S_w is presented alone, a response R_w , different from R_c , is produced, and R_w in turn results in some response R_2 , which may or may not be the same as R_1 . S_w may become conditioned to R_2 .

When both stimuli S_c and S_w are presented simultaneously, then under certain conditions a choice must be made, as only one of the responses, R_c or R_w , can be made. When they have both been presented, the conditioning centers M and M' (Rashevsky, 1938, chap. xxiv) maintain an excitation acting on C and C' respectively after S_c and S_w are discontinued. We assume that C (and C') represents many

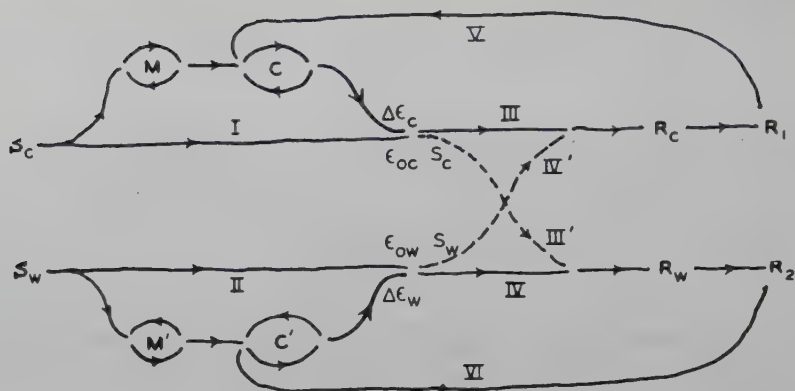


FIGURE 1

circuits having a distribution in thresholds, but that none of them becomes excited unless acted upon by M and V (M' and VI) simultaneously. This part of the mechanism is the essential part of the mechanism discussed by Rashevsky, (1938) and determines the strength of the conditioning [equation (1)] due to additional elements of C coming into play with each response R_c . The fiber from R_1 , V , is so drawn to indicate that the response R_c is in itself a stimulus.

The centers M and M' represent many elements having a distribution of thresholds. As is implied above, we assume that certain of these elements become excited by S_c alone, and that number increases with S_c . But if the state of excitation could be permanently maintained at a constant level, the time, t , between presentation of S_c and the response R_1 would not enter into the expression for the strength of the conditioned response as it must. Let us therefore assume that the centers come under inhibitory influences which thus tend to remove the centers from the steady state of excitation, that is, inhibitory fibers from various centers act upon M . If these inhibitory effects at one of the elements M_i exceeds some value h_i , the threshold of stability of M_i , then M_i no longer contributes to the excitation acting on C . Thus the strength of the excitation acting on C decreases with the time t . Let x be proportional to the random influence (inhibitory minus excitatory factor) acting to disrupt M . If $q(x)$ is the probability for a certain x , the chance that those thresholds less than h will be disrupted is given by z , the integral of $q(x)$ from h to ∞ . But if the value of x changes, on the average, every τ seconds, then the time t required to eliminate those circuits of thresholds less than h is given by $t = \tau/z$. Hence, as z is a function of h , h is a function of t . But the number of elements acting was originally equal to the integral of the distribution function of the thresholds from zero to

the maximum (depending on S_c). Now after a time, t , the number of circuits acting is given by the integral from $h(t)$ to the maximum. Thus the number of elements acting is obtained as a function of t , given the distribution functions. As the number of elements acting determines the strength of the conditioned response, we see that the latter is a function of t , [equation (1)] and this relation can be obtained for any specified case.

The strength of a positively conditioned response, R , will depend on the number of trials, n , and upon the time, t , between the unconditioned and conditioned stimuli, as well as upon other factors. It is almost axiomatic that R will increase monotonically with n , at least over a very wide range. N. Rashevsky (1938, chap. xxv) has discussed a mechanism of conditioning and obtains R as an exponential function of n , in which R is zero for n equal to zero and R increases to a limit as n becomes infinite. The coefficient of the n in the exponent contains the stimulus strength of the unconditioned stimulus. Assuming that, centrally, this value decays exponentially with time, (Rashevsky, 1938, chap. xxvii) we could obtain the function $R(n, t)$. More generally we can write for $R(n, t)$ an expression of the form

$$R(n, t) = \phi(t) [1 - e^{-an\psi(t)}]. \quad (1)$$

We shall, however, use only the first term of the expansion of the exponential in our present discussion. Then, if

$$f(t) = \phi(t) \psi(t), \quad (2)$$

we have the approximation to equation (1)

$$R(n, t) = a n f(t). \quad (3)$$

Instead of presenting a single unconditioned stimulus, let two stimuli be presented, one of which is to be conditioned to the response desired, thus referred to as the "correct" stimulus, S_c , and a second stimulus which is not to be conditioned and referred to as the "wrong" stimulus, S_w (Figure 1). Let c be the cumulative number of correct responses or responses to the correct stimulus, and let w be the number of wrong responses. For the present, we shall not consider failures to respond or other possible responses, so that, if n is the total number of responses, (hereafter referred to as the number of trials) then

$$n = c + w. \quad (4)$$

The derivative of c with respect to n is the proportion of correct responses for the particular values of c and n . Thus, defining P_c as

the probability of a correct response for given values of c and n , we may identify the probability predicted with the proportion observed by writing

$$P_c = \frac{d c}{d n} ; \quad (5)$$

and similarly

$$P_w = \frac{d w}{d n} , \quad (6)$$

where P_w is the probability of a wrong response. From the nature of our restrictions and from an inspection of equations (4), (5) and (6), it is evident that $P_c + P_w = 1$.

Let the value of the excitation factor, ε , (Rashevsky, 1938, chap. xxii) corresponding to the stimuli S_c be ε_{oc} (synapse s_c , Figure 1). Similarly let ε_{ow} be the value of ε corresponding to S_w . Let $\Delta \varepsilon_c$ be the amount of ε at synapse s_c from center C due to the conditioning between S_c and the response R_c . Also let $\Delta \varepsilon_w$ be the amount at s_w from C' due to conditioning of S_w with R_w . If $\varepsilon_c = \varepsilon_{oc} + \Delta \varepsilon_c$ is the total amount at synapse s_c , and $\varepsilon_w = \varepsilon_{ow} + \Delta \varepsilon_w$ is the total amount at synapse s_w , then, if fibers III, III' IV, and IV', have the properties necessary for a discriminating mechanism (Landahl, 1938a), the quantity $\varepsilon_c - \varepsilon_w$ plays the role of $\varepsilon_1 - \varepsilon_2$ in that development. Using those results we have [Landahl 1938a, equation (10)],

$$\log 2 P_w + k(\varepsilon_c - \varepsilon_w) = 0 . \quad (7)$$

So far we have considered only the possibility of two stimuli being responded to. For the more general case of N stimuli, we must correct P_c for chance by introducing [Landahl, 1939, equation (29)],

$$P = \frac{N}{N-1} \left(P_c - \frac{1}{N} \right) \quad (8)$$

where P is the probability of a correct response corrected for chance. Then introducing the above value of P into equations (15) and (10), (Landahl, 1938) we obtain instead of equation (7), the more general relation

$$\log \frac{N P_w}{N-1} + k(\varepsilon_c - \bar{\varepsilon}_w) = 0 . \quad (9)$$

where $\bar{\varepsilon}_w$ is the average value of ε_w for the $N-1$ wrong stimuli. A discussion of equation (9) and a comparison with data obtained for its verification will be given in a subsequent paper. For the present we shall consider the case for which $N = 2$, that is, we shall refer to equation (7).

2. *Preliminary applications to maze learning.* Let the stimuli presented be conditioned to some response which we shall refer to as the goal. Let a stimulus S_i , an alley entrance, lead to a goal where the goal response is elicited. $R_i(n_i, t_i)$ is the strength of the response produced by stimulus S_i because of its association with the goal n_i times. t_i is the average time which elapses between presentation of S_i and the beginning of the goal response. The stimulus S_i , after the initial trial, is no longer the same stimulus as far as the fibers *III*, *III'*, *IV*, *IV'* of Figure 1 are concerned, since instead of an initial excitation factor ε_{i0} being produced, a larger value $\varepsilon_i = \varepsilon_{i0} + \Delta\varepsilon_i$ is produced because of the past trials. But $\Delta\varepsilon_i$ is proportional to $R_i(n_i, t_i)$. Hence we may write

$$\varepsilon_i = \varepsilon_{i0} + \eta R_i(n_i, t_i) \quad (10)$$

where η is a proportionality constant. Then introducing equation (3), we have

$$\varepsilon_i = \varepsilon_{i0} + B n_i f(t_i), \quad (11)$$

where $B = a\eta$, n_i is the number of responses of S_i , and t_i is the value of t when response is made to S_i .

Let a stimulus S_p be the entrance to a blind alley. Consider that the return response is conditioned to S_p , so that the response to enter is decreased. (Rashevsky, 1938, chap. xxviii, Landahl, 1938b). The values of ε_p , corresponding to S_p , will again be conditioned to the goal by an amount $B n_p f(t_p)$, but at the same time will be decreased by an amount $F n_p f(t_p)$. Here t_p is the time elapsing between presentation of S_p , and the goal response including the time $2t_{p1}$, required to travel into the blind and back. The coefficient F corresponds to B , but is not necessarily the same, as different responses are being conditioned. Also, n_p is the number of responses to S_p . Then we have

$$\varepsilon_p = \varepsilon_{op} + B n_p f(t_p) - F n_p f(\varepsilon_{p1}). \quad (12)$$

Hereafter we shall assume for simplicity that $\varepsilon_{oi} = \varepsilon_{op}$, unless otherwise stated. This is equivalent to assuming that responses to S_i and to S_p are equally probable before conditioning has taken place. In order to continue the development, it is evidently necessary to use the mean values for the various times t . We shall also assume that, on the average, the velocity of travel is a constant. This does not at all imply that the length of time of running a maze is constant through successive trials.

3. *Two routes to a goal response.* In this section we confine the discussion to the case in which there are two separate paths to the

goal. Let a response to one of the paths, designated by the subscript c , be called a correct response, so defined because $t_c < t_w$, i.e. the correct path requires shorter time to traverse. Then from equation (11) we have for ε_c and ε_w

$$\varepsilon_c = \varepsilon_{oc} + Bcf(t_c), \quad (13)$$

$$\varepsilon_w = \varepsilon_{ow} + Bwf(t_w), \quad (14)$$

where c and w are again the numbers of correct and wrong responses, and $c + w = n$, the number of trials. The possibility of retracing is not considered here.

Substituting equations (13) and (14) into (7) and recalling that $\varepsilon_{oc} = \varepsilon_{ow}$, and $c + w = n$, then introducing (6), we obtain a differential equation which may be integrated and solved for w :

$$w = \frac{1}{k B [f(t_c) + f(t_w)]} \times \log \frac{2 f(t_c)}{f(t_c) - f(t_w) + [f(t_c) + f(t_w)] e^{-kBf(t_c)n}}. \quad (15)$$

The initial conditions are taken as $w = c = n = 0$. Unless forced trials are given in advance, these conditions are true. Equation (15) is a two parametric curve, the parameters being $kBf(t_c)$ and $kBf(t_w)$. The initial slope is one-half. The curve increases to a limit, which is a function of both parameters. In order that the limit exist, we must have $f(t_c) > f(t_w)$. But $t_c < t_w$, and hence $f(t)$ must decrease with t .

We shall here consider only the case in which $f(t)$ is given by a simple decreasing exponential (Rashevsky, 1938, chap xxviii):

$$f(t) = g e^{-\alpha t}, \quad (16)$$

where α and g are constants. Then the value of w for $n = \infty$, w_∞ , may be written

$$w_\infty = \frac{1}{k B g (e^{-\alpha t_c} + e^{-\alpha t_w})} \log \frac{2 e^{-\alpha t_c}}{e^{-\alpha t_c} - e^{-\alpha t_w}}. \quad (17)$$

The value, w_∞ , is essentially the total number of errors required in learning a task to more or less perfection, an empirical value very often used. Expanding (17) we have very roughly, for $t_c \propto t_w$,

$$w_\infty \propto \frac{[1.69 - \alpha(t_w - t_c)] e^{\alpha t_c}}{2 k B g} \quad (18)$$

so that the total number of errors made roughly decreases linearly with the time difference in the paths and increases as an exponential

of the average time length of the paths. Thus, for rapid elimination the paths must be as short and as different in length as possible.

Equation (15) has an upper limit for w . In some instances, at least, such will not be the case. If, instead of equation (3) we had used equation (1), the resulting $w(n)$ relation would not have had this property. The $w(n)$ relation cannot be solved explicitly. For large values of w and n , we can obtain the slope $(d w / d n)_\infty$

$$\left(\frac{d w}{d n} \right)_\infty = \frac{1}{2} e^{-\frac{B \kappa}{a} [\phi(t_c) - \phi(t_w)]} \quad (19)$$

Since the slope cannot exceed one-half, we must have $\phi(t_c) > \phi(t_w)$, and as $t_c < t_w$, then $\phi(t)$ must decrease with t . If this final slope is very small, we may use equation (15) throughout with good approximation. Gulliksen (1934) has discussed a curve which has an asymptote which is not horizontal (cf. also Gulliksen and Wolfle, 1938).

4. *Elimination of a blind alley.* Consider the case in which two entrances are presented, S_w to a blind and S_c to the goal. We shall not consider retracing so the subject either responds directly to the S_c and proceeds to the goal, or responds to S_w in which case he goes down the blind and back, then necessarily proceeds to the goal. Thus retracing must be prevented in an experiment if we are to check the following results. Let t_1 be the time taken in traveling directly to the goal and let t_2 be the time taken to reach the end of the blind. Then from equation (11) we have

$$\varepsilon_c = \varepsilon_{oc} + B(c + w) f(t_1) \quad (20)$$

as we replace i by c and n_i by $c + w$, and t_i by t_1 for this case. Whether a wrong or correct choice is made, the goal response is eventually obtained.

For ε_w we have from equation (12)

$$\varepsilon_w = \varepsilon_{ow} + B w f(t_1 + 2t_2) - F w f(t_2) \quad (21)$$

as we replace n_j by w , subscript j by w , and since $t_{j1} = t_2$, and $t_j = t_1 + 2t_2$.

Using equations (20) and (21) instead of (13) and (14) we obtain instead of equation (15) the expression, if $\kappa = F/B$,

$$w = \frac{1}{k B [f(t_1 + 2t_2) - \kappa f(t_2)]} \log \{ 2 f(t_1) / [2 f(t_1) - f(t_1 + 2t_2) + \kappa f(t_2) + (f(t_1 + 2t_2) - \kappa f(t_2)) e^{-\kappa B f(t_1) n}] \} \quad (22)$$

for

$$f(t_1 + 2t_2) - \kappa f(t_2) \geq 0,$$

or

$$w = \frac{1}{2 k B f(t_1)} (1 - e^{-k B f(t_1) n}) \quad (23)$$

for

$$f(t_1 + 2t_2) - \kappa f(t_2) = 0.$$

Equation (22) is a two parametric equation where the two parameters are $k B f(t_1)$ and $\{k B f(t_1 + 2t_2) - k F f(t_2)\}$. As the t 's are experimental values, the only parameter which enters here and not in equation (15) is F . If t_1 in this case is made equal to t_c in the previous equation, then one of the composite parameters is the same for the two situations. Whether or not this requirement is so could be verified experimentally.

The limiting value of w , w_∞ , when equation (16) is used, is given by

$$w_\infty = \frac{1}{k B g (e^{-a(t_1+2t_2)} - \kappa e^{-at_2})} \log \frac{2 e^{-at_1}}{2 e^{-at_1} - e^{-a(t_1+2t_2)} + \kappa e^{-at_2}}, \quad (24)$$

or

$$w_\infty = \frac{e^{at_1}}{2 k B g}$$

corresponding to (22) and (23). In the second equation (24), w_∞ evidently increases with t_1 , but a change in t_1 implies a change in t_2 because of the restriction for this case. In the first equation (24), w_∞ increases with t_1 if t_1 is large enough. That is, the number of total errors increases for increased distance to the goal, provided that this distance is sufficiently large. (cf. Hull, 1934).

For a constant B , κ is proportional to F , the coefficient determining the rate of conditioning of the return response at the alley end to the entrance to the blind. It might be expected that w_∞ would decrease with increasing values of F and hence κ . However, for sufficiently large values of t_2 and sufficiently small values of t_1 , w_∞ decreases with κ .

The variation of w_∞ with t_2 is complex. For large enough values of t_1 , w_∞ increases with increased t_2 . But, if t_1 is small enough and if κ is small enough, w_∞ decreases as t_2 increases. Thus, if κ is sufficiently small, the elimination of a blind will take more trials for a longer blind if the goal is far enough away, but if the goal is close enough, elimination of the blind will take fewer trials for a longer blind. This result has been mentioned previously (Landahl, 1938b,

Figure 2) where a qualitative comparison with experimental data (Peterson, 1917) is given. If κ has a value small enough for such an effect to be present, the effect could be eliminated by increasing κ , either larger F or smaller B . Decreased hunger would mean decreased effect of the goal response and hence smaller B or larger κ . Thus less hungry animals might well show an opposite effect, eliminating the longer blinds with more difficulty even near the goal. Such an effect was pointed out (Landahl, 1938b, p. 178) to be a possible contributing factor in the data by Tolman, et al. (1930) where such a result was found.

We have been considering only a one unit maze. Each unit of a maze can be treated in the same way so that we may obtain the variation of w with n at each junction. Two difficulties arise. First, the time to the goal decreases with successive trials, and that differently for the various junctions in the maze. However, since this time variation can be predicted theoretically and determined empirically, it can be taken into account. In the second place, there enters another factor which may be too large to neglect. An animal which is accustomed to mazes may have learned to attribute a positive value to a correct path because a blind alley is thus avoided. In this case, conditioning could take place not only with the goal response but with the learned response due to having successfully avoided a blind. Such an effect would be especially noticeable far from the goal and would decrease the number of errors from that otherwise predicted. This factor would considerably complicate the results.

Even with these two difficulties overcome, we should predict that the last alley of a maze would require the same number of errors for elimination regardless of the number of blinds in the maze. If there is an inhibitory effect from the conditioning centers C and C' for one junction due to those of other junctions, then an increase in the complexity of the maze would tend to increase the number of errors for elimination at each junction. Data by Peterson (1917) indicate fairly strongly that the last blind of a long maze is more difficult to eliminate than the last blind of a shorter maze. The last two alleys in each of two mazes were equidistant from the goal. Using the averages from the last two alleys in each case, and using the totals of all animals on the two sets of experiments, the following values are obtained: for the six alley maze, the average number of errors for the last two alleys is 24, while for the ten alley maze the corresponding value is 32. A rough estimate gives the standard error a value of four, so that the critical ratio is about two.

With the above factors accounted for, we should be in a position to predict, for any maze, the number of errors for a given number of

trials at each junction of the maze. This would include the number of errors for elimination of each of the blinds. In order to attempt such a prediction, it would be necessary to know the dimensions of the maze and sufficient experimental values to determine the parameters. It would also be necessary to know that such factors as left-right bias, directional preferences, etc. be properly eliminated or accounted for.

5. *Elimination of a return alley.* Let us now consider one unit of a return maze (Landahl, 1938b, Figure 3). We shall assume that experimental arrangements eliminate the possibility of retracing. We first restrict our discussion to the situation in which only one of the entrances to the return alley can be entered, so that there is but one correct and one wrong response possible. Let t_1 be the time taken to reach the goal if the correct alley is chosen. Let t_2 be the time taken to return to the start if the return alley is chosen. Then from equation (11), we have for ε_c and ε_w the expressions

$$\begin{aligned}\varepsilon_c &= \varepsilon_{oc} + B(c + w)f(t_1), \\ \varepsilon_w &= \varepsilon_{ow} + Bwf(t_1 + t_2).\end{aligned}\tag{25}$$

In each trial, whether the return alley is entered, contributing to w , or the correct alley is entered, contributing to c , the correct alley is entered and conditioning takes place. Introducing (25) into (7) and using (6) then integrating we obtain

$$w = \frac{1}{k B f(t_1 + t_2)} \log \frac{2 f(t_1)}{2 f(t_1) - f(t_1 + t_2) + f(t_1 + t_2) e^{-k B f(t_1) n}}.\tag{26}$$

Using (16) we have for the limit of w ,

$$w_\infty = \frac{e^{a(t_1+t_2)}}{k B g} \log \frac{2}{2 - e^{-a t_2}}.\tag{27}$$

Thus the total number of trials for elimination of the return increases exponentially with the distance to the goal; whereas it increases with increased length of the return alley if this length is long enough, but decreases with increased length of the return alley if this length is small enough. Thus there is one minimum so that a certain length of the return alley will give most efficient elimination. But this length may be too small to be detected. This result may seem implausible, but it may be pointed out that for $t_2 = 0$, (no alley) $w_\infty = \infty$ (i.e., no elimination), but as a wrong and correct response cannot be differentiated there is no contradiction. In this case we have introduced no new symbols not found in equation (15), except the t 's which are measurable.

If now, instead of preventing entrance to one of the return alley entrances, we allow either to be entered as well as the goal entrance, but again prevent retracing, we will have the same values for ε_c and ε_w as are given in equation (25). Now, instead of using equation (7) we use equation (9) with $N = 3$, there being three choices possible. Assuming that the wrong responses are equally probable so that $\bar{\varepsilon}_w = \varepsilon_w$, we have

$$w = \frac{1}{k B f(t_1 + t_2)} \times \log \frac{3f(t_1)}{3f(t_1) - 2f(t_1 + t_2) + 2f(t_1 + t_2) e^{-kBf(t_1)n}} \quad (28)$$

for which, using (16)

$$w_\infty = \frac{e^{+a(t_1+t_2)}}{k B g} \log \frac{3}{3 - 2e^{-at_2}} \quad (29)$$

Since the same parameters occur in equations (28) and (29) as occur in (26) and (27), except for the numbers 2 and 3, we can predict completely the behavior from one situation to the other. Whether or not the prediction is sufficiently accurate could be tested experimentally.

It will be noted that, on the basis of this mechanism, elimination is essentially abrupt as compared with the previous mechanism in which there was gradual elimination. Here we consider only two possibilities, entrance or no entrance. However, it can be seen that the probability of a chance fluctuation being able to produce the return response before the alley end is reached would be larger with successive trials. This point requires a more detailed study.

6. *Application to the Lashley jumping apparatus.* Let a pair of stimuli be presented such that, if response is made to one after time t_c , a reward is obtained, where as if the other stimulus is responded to, after a time t_w , an unpleasant response follows. Then we have

$$\varepsilon_c = \varepsilon_{oc} + B' c f(t_c), \quad (30)$$

$$\varepsilon_w = \varepsilon_{ow} - B'' w f(t_w), \quad (31)$$

where the B 's are in general different from each other and different from the B in the previous cases. The sign in equation (29) is negative as we assume that the result of the wrong response tends to be avoided.

In this case, for illustration, let us permit ε_{ow} and ε_{oc} to have separate values. For simplicity let $t_c = t_w$. Setting

$$\Delta = e^{k(\varepsilon_{oc} - \varepsilon_{ow})} \quad (32)$$

and using (6) and (7) we obtain

$$w = \frac{1}{k(B' - B'')f} \log \frac{2\Delta B'}{2\Delta B' - (B' - B'')(1 - e^{-B'kf n})} \quad (33)$$

for $B' \geq B''$, and

$$w = \frac{1}{2k B' f \Delta} (1 - e^{-k B' f n}) \quad (34)$$

for $B' = B''$.

The value of Δ is half of the reciprocal of the initial slope, and hence is readily determined by the initial responses. With Δ obtained, then by equation (32) we have $k(\varepsilon_{oc} - \varepsilon_{ow})$, that is, we have a measurement of the difference in ε values for the stimuli (Landahl, 1939, p. 163).

Equation (33) is a three parametric curve, the parameters being Δ , $k B' f$ and $k B'' f$. The value of Δ is determined from the initial slope but the other two parameters are not so easily determined. Although three parameters give more freedom than we might desire, it should be noted that it is not in general possible to fit this curve to any set of data such that the initial slope is correct, that the limiting value is correct, and that the curve passes through some arbitrary point in the middle region of the curve. And even where this is possible, there is no assurance that the parameters will be positive. It is also necessary that the values of B' and B'' vary appropriately with change in reward and punishment. Similarly for the more general case in which $t_c \neq t_w$, a change in either t , or both t 's should have the predicted effect upon the parameters. A complete check of the theory requires a large amount of data. So, conversely, if agreement is obtained, the theory unifies a great number of facts.

That the general shape of the errors-trials relation is correct may be shown by comparison with data. In Figure 2, the experimental values are by Gulliksen (1934) for rats number (1) and (13), and the curves are graphs of equation (33) with $\Delta = 1$, $k B' f = .0121$, $B'' = 0$ and $\Delta = .63$, $k B' f = .0229$, $B'' = 0$ respectively. Assuming the linear relationships of equation (30) and (31) to be correct, this implies that the effect of the wrong response on the learning is negligible compared with that of the correct response. According to Gulliksen's formulation, the ratios of the effectiveness of the wrong response to that of the correct response are 4 and 1.1 in these cases. It should be possible to determine experimentally which predictions are

best. If the present formulation is shown to be wrong in this respect, or if it is found not to fit the $w(n)$ curves well enough, the only appreciable change that can be made is the replacement of equations (30) and (31) by more exact expressions.

We have based the above development upon the mechanism represented in Figure 1. However, it is possible to proceed on a more formal level (cf. Thurstone, 1930, 1933). A very desirable starting point for a development analogous to that given above would be some law of the effect of reward and punishment (Gulliksen, 1934) together with the law of comparative judgment (Thurstone, 1927, cf. also Gulliksen and Wolfle, 1938). For the case of two choices this can be done. But for more than two choices a generalization of the law to

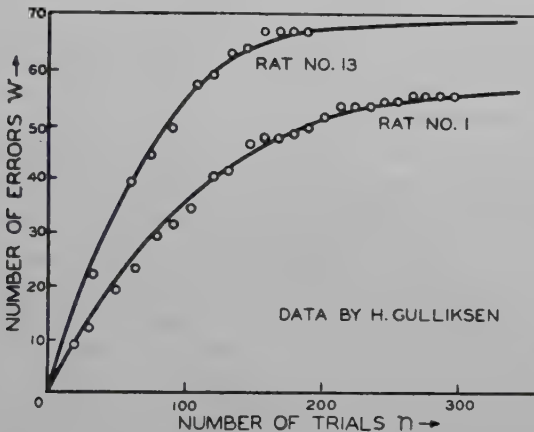


FIGURE 2

the case in which $N > 2$, (or some approximation) would be desirable, and this generalization presents some difficulties. As the slopes of the learning curve give proportions of judgments for any trial n , the scale values corresponding could be obtained from the generalized law, and thus the relation between the scale value and the number of trials would be obtained. One should expect that this relation would be independent of a large number of variables. If so, application could be made to specific cases, as above, obtaining analogous expressions. The present development is formally more similar to those mentioned above than is perhaps apparent.

A comparison of the above equation (15) with Thurstone's learning curve involving the same variables gives the parameters of the latter curve, a , \sqrt{m} and k the following meanings — a is the reciprocal of the initial slope and would be $N/(N-1)$ where N is the number of possible paths (two in the case treated); m is inverse with the dif-

ferences in length of the paths; and k is proportional to the quantity $g B k$. The parameter, α , of equation (16) enters in a rather complicated manner into this comparison preventing a clear cut separation into two parts, but the above is essentially correct. Thus, as it will be noticed, m is essentially a parameter of the task while k is a parameter of the individual as was defined. To this extent the present formulation is substantiated by data which bears out such a separation in Thurstone's formulation (cf. Wiley and Wiley, 1937).

The mechanism of Figure 1 is, of course, too simple, but is still able to predict some basic relationships. It would be desirable also to have it predict a number of other relationships, particularly the properties that are formulated by Gulliksen & Wolfe (1938), such that predictions can be made for specific types of stimuli and stimulus relationships.

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MATHEMATICAL BIOPHYSICS OF CELLULAR FORMS AND MOVEMENTS

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Rashevsky's equations for describing the joint variation of cell shape and concentration of a metabolite are discussed. Conditions for the existence of non-spherical equilibria and the location of these are obtained and involve only two parameters a and A . Sufficient (but not necessary) conditions for the stability of these equilibria can also be expressed in terms of these parameters alone. Necessary conditions involve in some cases a third parameter B . Quasi-periodic fluctuations about a stable nonspherical equilibrium may occur, but only in case B lies on a certain finite range which can be defined in terms of a and A .

1. *The problem.* Rashevsky (1939; 1940, chap. v) has employed his approximation method to derive the equations describing the deformation of a cell and the variation of the "average" internal concentration of a metabolite in the particular case where the permeability of the cell for this metabolite is infinite and where the cell volume remains constant. With these equations, he shows that, besides sphericity, which is always an equilibrium shape, there will be either two others, or no others, according to the relations among the physical constants involved. For the special case when the internal diffusion coefficient is much greater than the external diffusion coefficient, more complete information as to the occurrence and nature of these equilibria was obtained.

We wish here to employ a transformation by means of which the equations can be simplified and their discussion facilitated. From this transformation will be obtained the exact equations, readily solvable, for locating these equilibria when they occur, and the exact relations which are needed to characterize them.

The equations in question are the following (Rashevsky, 1940, chap. v, equations (2) and (3)):

$$\frac{dc}{dt} = q - \frac{3D_i D_e r_2^2 (D_e + 2D_i) + 2(r_1 D_e + 2r_2 D_i) r_1}{r_1 r_2^2 (r_1 D_e + 2r_2 D_i) (D_e + 2D_i)} c, \quad (1)$$

$$\frac{1}{r_1} \frac{dr_1}{dt} = \frac{3RT\mu}{2M\eta} \frac{D_i D_e (r_1 - r_2)}{(2r_2 D_i + r_1 D_e) (2D_i + D_e)} c - \frac{\gamma}{2\eta} \frac{r_1 - r_2}{r_1 r_2}. \quad (2)$$

For the notations the reader is referred to the source mentioned. We point out, however, that the cell is regarded as a spheroid with polar radius r_1 and equatorial radius r_2 . All other symbols refer to constants, except, of course, t and c , the latter symbol representing the excess of the average internal concentration of the metabolite over the external concentration at infinity.

To simplify these equations somewhat, we introduce the symbols ρ , x , and y :

$$\rho^3 = r_1 r_2^2, \quad y = x^3 = r_1 / r_2, \quad (3)$$

ρ being the radius of the sphere of equal volume, supposed to be constant, y being the ratio of polar to equatorial radius. The introduction of x , the cube root of this ratio, is for the purpose of rationalizing the differential equations. From equations (3) it follows that

$$r_1 = \rho x^2, \quad r_2 = \rho / x. \quad (4)$$

For further simplification of notation we introduce the following symbols

$$a = \frac{2D_i}{D_e}, \quad A = \frac{RT \rho^3 \mu q}{4M \gamma D_i}, \quad B = \frac{12\eta D_i}{\gamma \rho (a+1)}, \quad \Gamma = \frac{q \rho^2 (a+1)}{9D_i}. \quad (5)$$

When these substitutions are made, we obtain the equations

$$\frac{dx}{dt} = \frac{q}{3B\Gamma} \left(\frac{2aA}{3\Gamma} \frac{x}{x^3 + a} c - \frac{1}{x} \right) (x^3 - 1), \quad (6)$$

$$\frac{dc}{dt} = \frac{q}{3\Gamma} \left(3\Gamma - \frac{2x^6 + 2ax^3 + a + 1}{(x^3 + a)x} c \right), \quad (7)$$

equivalent to the pair (1) and (2).

2. *Determination of the equilibria.* An equilibrium configuration is determined by a pair of values, x and c , or y and c , which cause the left members of (6) and (7) to vanish.* It is sufficient to know the value of x or y at any equilibrium in order to be able to calculate the value of c , so that we shall speak, for brevity, of the equilibrium ratios y , meaning by this the value of the ratio y of the polar to the equatorial radius of the cell when the cell is in a state of equilibrium. Or we shall speak of a spherical equilibrium, of a prolate spheroidal equilibrium, or an oblate spheroidal equilibrium according to the geometrical form of the cell in the equilibrium in question.

* The mathematical theory of equilibrium or "critical" points of a system of ordinary differential equations, which is presupposed here, can be found in various places, among which may be mentioned Bendixson (1901).

Since for $x = 1$, the right member of (6) vanishes independently of the value of c , it follows that the sphere is always an equilibrium shape. The corresponding value of c is obtained by setting the right member of (7) equal to zero, with $x = 1$, and solving for c . This gives $c = \Gamma$. In order to study the equations in the neighborhood of this equilibrium we set

$$x = 1 + \xi, \quad c = \Gamma + \eta \quad (8)$$

and expand in powers of ξ and η . We retain only the first order terms, and find

$$\frac{d\xi}{dt} = \frac{q}{B\Gamma} \frac{2aA - 3(a+1)}{3(a+1)} \xi + \dots, \quad (9)$$

$$\frac{d\eta}{dt} = \frac{q}{\Gamma(a+1)^2} [a(a+3)\Gamma\xi - (a+1)^2\eta] + \dots. \quad (10)$$

The characteristic roots of the approximating linear equations are

$$\lambda_1 = \frac{q}{B\Gamma} \frac{2aA - 3(a+1)}{3(a+1)}, \quad \lambda_2 = -\frac{q}{\Gamma}. \quad (11)$$

The only parameter in the original equations (1) and (2) which can be negative is q , and since A and Γ both contain q as a factor, their signs will be the same as that of q . Since $q > 0$ during production, $q < 0$ during consumption of the substance being metabolized, and since the conditions for an equilibrium to be stable is that λ_1 and λ_2 shall both be negative, it is at once evident that *when the essential metabolic activity of the cell is that of the consumption of some substance, the spherical equilibrium is always stable; when it is that of production of some substance, then the spherical equilibrium is stable whenever*

$$A < \frac{3(a+1)}{2a}. \quad (12)$$

In no case is the occurrence of quasi-periodic oscillations (approach to the equilibrium configuration by a spiral path in the (x, c) - plane) possible in the neighborhood of the spherical equilibrium. Here and hereafter we neglect all consideration of limiting cases where some relations of inequality among the parameters are replaced by equalities.

The non-spherical equilibria, when they exist, are given by setting the right members of (6) and (7) equal to zero, with $x \neq 1$. This gives

$$c = \frac{3\Gamma(x^3 + a)x}{2x^6 + 2ax^3 + a + 1}, \quad c = \frac{3\Gamma(x^3 + a)}{2aA x^2}. \quad (13)$$

By equating the right members of these two equations, and suppressing all factors which are essentially non-null, we obtain the equation

$$\phi(y) \equiv 2y^2 - 2a(A - 1)y + a + 1 = 0 \quad (14)$$

for the determination of the non-spherical equilibrium ratios.

When $q < 0$, then $A < 0$, and equation (14) has no positive roots. Hence, *when the essential metabolic activity of the cell is that of consumption of a metabolite, there can exist no equilibrium state apart from the spherical one.* There is therefore nothing more to be said of the case of consumption, and we now confine our attention to the case $q > 0$, when all parameters are positive.

Either two non-spherical equilibria may exist, or else there are none. Evidently if there are two, the roots of (14) must be positive, and therefore $A > 1$. This condition is necessary, but the necessary and sufficient condition for the roots of (14) to be real and positive is this and the added condition that the discriminant be positive. It follows that *two non-spherical equilibria exist when and only when*

$$A > \frac{a + \sqrt{2(a+1)}}{a}.$$

Otherwise there are none.

If $\phi(1) < 0$, then two non-spherical equilibria exist, one being oblate spheroidal, and one prolate spheroidal. But this occurs when and only when (12) fails. Hence we can say that *the spherical equilibrium is always stable unless there exist both a prolate spheroidal and an oblate spheroidal equilibrium.* If (12) is satisfied and there exist two non-spherical equilibria, then both are oblate, or else both are prolate. In the former case, both equilibrium ratios are exceeded by unity, and hence their product is less than unity. In the contrary case, the product exceeds unity. From (14) it appears that these two conditions are equivalent to $a < 1$ and to $a > 1$, respectively. Hence, *when two non-spherical equilibria exist, one of these is oblate, and the other prolate unless (12) is satisfied. But if (12) is satisfied, then both are oblate when $a < 1$, and both are prolate when $a > 1$.* It is important to note that the existence and location of the non-spherical equilibria is determined by the physical parameters in the combinations a and A alone, as these are defined by (5). *A priori*, when other things are held fixed, a high metabolic rate, or a large cell size, or a high temperature will always assure the existence of these equilibria.

The conditions for the occurrence of the various cases is illus-

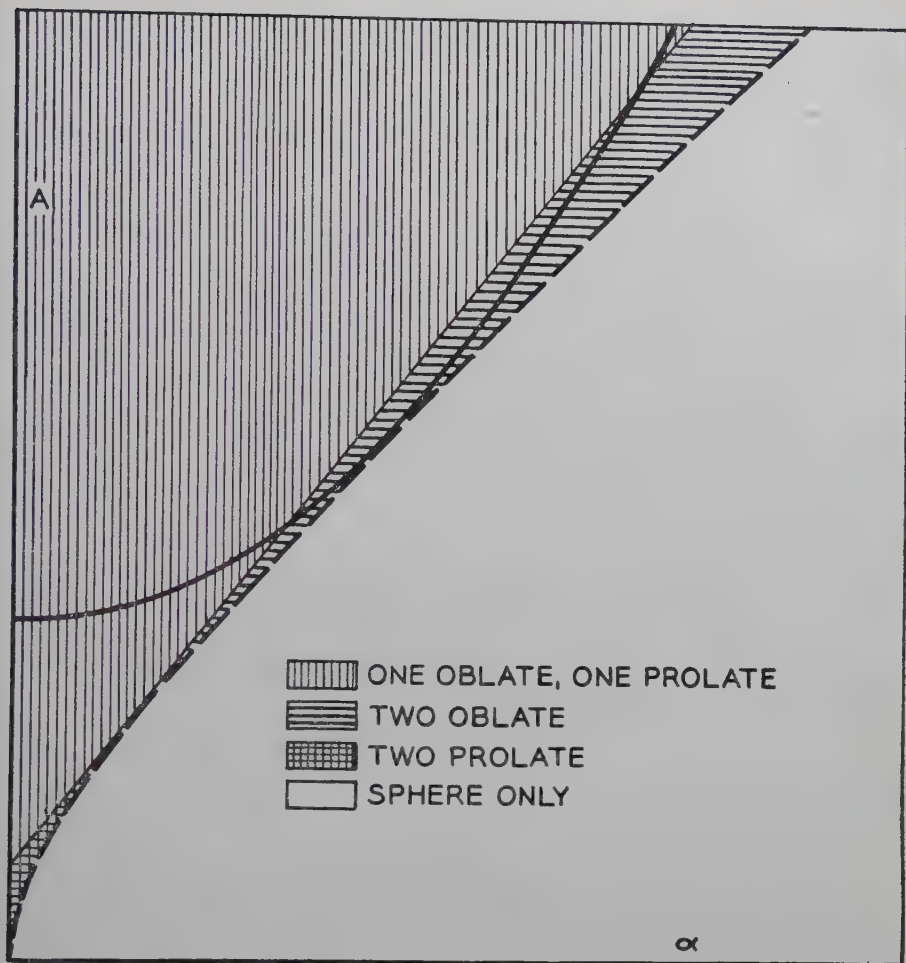


FIGURE 1

This figure represents qualitatively the regions of the (α, A) plane with which the various equilibria are associated. A scale drawing of this size fails to separate visibly the curves on a drawing.

trated in the figure. Two of the curves represented are branches of the curves

$$4\left(\alpha + \frac{1}{2}\right)^2 - 2(A - 1)^2 = 1, \quad 3\alpha - 2A + 3 = 0 \quad (15)$$

$$\alpha \equiv 1/a.$$

The other will be discussed later. The first curve is a hyperbola whose center is at $(-1/2, 1)$; the second is a straight line which is tangent to the hyperbola at the point $(1, 3)$. The two non-spherical equilibria exist and are of opposite types when the point (α, A) lies above the

straight line; they do not exist when the point lies below the upper half of the right-hand branch of the hyperbola. When the point lies between the straight line and this arc of the hyperbola, the equilibria exist and are alike in type; both are prolate spheroids when the point lies below the point of tangency, both are oblate when the point lies above the point of tangency.

3. *Conditions for stability and periodicity.* Though the parameters a and A alone determine the location of the non-spherical equilibria, they do not in all cases determine whether they are stable or unstable. To investigate the character of these equilibria, we shall expand the equations about each of the equilibrium values. It is inconvenient, however, to express these equilibrium values in terms of a and A . Consequently, supposing the equilibria to exist, we express A in terms of a and the value x_1 of x at one of them. If x_1 is the value of x at one of these equilibria, then $y_1 = x_1^3$ satisfies (14), and therefore

$$2aA = \frac{2x_1^6 + 2ax_1^3 + a + 1}{x_1^3}. \quad (16)$$

Since the product of the roots of (14) is $(a + 1)/2$, therefore the value of x_2 at the other equilibrium satisfies

$$2x_1^3 x_2^3 = a + 1. \quad (17)$$

From (13) we have, then, that when $x = x_1$,

$$c = c_1 \equiv \frac{3\Gamma(x_1^3 + a)x_1}{2x_1^6 + 2ax_1^3 + a + 1}. \quad (18)$$

Hence if we set

$$x = x_1 + \xi, \quad c = c_1 + \eta \quad (19)$$

in equations (6) and (7) and expand, we obtain

$$\begin{aligned} \frac{d\xi}{dt} &= \frac{q(x_1^3 - 1)}{9BI^2(x_1^3 + a)x_1^2} \\ &\times [-3\Gamma(x_1^3 - 2a)\xi + (2x_1^6 + 2ax_1^3 + a + 1)\eta] + \dots, \end{aligned} \quad (20)$$

$$\begin{aligned} \frac{d\eta}{dt} &= \frac{-q}{3\Gamma x_1(x_1^3 + a)(2x_1^6 + 2ax_1^3 + a + 1)} [3\Gamma\{4x_1^9 + 8ax_1^6 \\ &+ 4(a^2 - a - 1)x_1^3 - a(a + 1)\}\xi + (2x_1^6 + 2ax_1^3 \\ &+ a + 1)^2\eta] + \dots, \end{aligned} \quad (21)$$

where only terms of first order have been given. The characteristic

roots, λ_1 and λ_2 , of these equations have the sum and product

$$\lambda_1 + \lambda_2 = \frac{-q[Bx_1(2x_1^6 + 2ax_1^3 + a + 1) + (x_1^3 - 1)(x_1^3 - 2a)]}{3B\Gamma x_1^2(x_1^3 + a)}, \quad (22)$$

$$\lambda_1 \lambda_2 = \frac{q^2(x_1^3 - 1)(2x_1^6 - a - 1)}{3B\Gamma x_1^2(x_1^3 + a)}, \quad (23)$$

and the discriminant of the characteristic equation is

$$\begin{aligned} (\lambda_1 - \lambda_2)^2 = & q^2\{[Bx_1(2x_1^6 + 2ax_1^3 + a + 1) + (x_1^3 - 1) \\ & \times (x_1^3 - 2a)]^2 - 12Bx_1(x_1^3 - 1)(x_1^3 + a)(2x_1^6 - a \\ & - 1)\}/9B^2\Gamma^2 x_1^4(x_1^3 + a)^2. \end{aligned} \quad (24)$$

The equilibrium is stable if and only if $\lambda_1 + \lambda_2 < 0$ and $\lambda_1 \lambda_2 > 0$, while periodic or quasi-periodic oscillations occur in the neighborhood in case it is also true that $(\lambda_1 - \lambda_2)^2 < 0$. We have therefore to investigate the circumstances under which, at any non-spherical equilibrium x_1 , these inequalities hold.

Define

$$B_0 \equiv \frac{-(x_1^3 - 1)(x_1^3 - 2a)}{x_1(2x_1^6 + 2ax_1^3 + a + 1)}, \quad (25)$$

$$C \equiv -B/B_0, \quad (26)$$

$$f(C) \equiv (C + 1)^2 - \frac{12C(x_1^3 + a)(2x_1^6 - a - 1)}{(x_1^3 - 2a)(2x_1^6 + 2ax_1^3 + a + 1)}. \quad (27)$$

Then a little calculation shows that the condition $\lambda_1 + \lambda_2 < 0$ is equivalent to the condition $B > B_0$, while the condition $(\lambda_1 - \lambda_2)^2 < 0$ is equivalent to $f(C) < 0$. We note that $f(C)$ becomes positively infinite with C , and that it is positive for $C = 0$. Hence either $f(C) > 0$ for all C , or else there exists a pair of values C_1 and C_2 such that for $C_1 < C < C_2$, it is true that $f(C) < 0$, while for all other values of C , $f(C) \geq 0$. Hence either $(\lambda_1 - \lambda_2)^2 > 0$ for all B , or else there exists a pair of values B_1 and B_2 such that for $B_1 < B < B_2$, it is true that $(\lambda_1 - \lambda_2)^2 < 0$, whereas for every other B , $(\lambda_1 - \lambda_2)^2 > 0$. We note, then, that $f(C)$ has a minimum at

$$C = C_0 \equiv + \frac{10x_1^9 + 14ax_1^6 + (4a^2 - 7a - 7)x_1^3 - 4a(a + 1)}{(x_1^3 - 2a)(2x_1^6 + 2ax_1^3 + a + 1)} \quad (28)$$

and that the minimal value is

$$f_{min} \equiv \frac{12(x_1^3 + a)(2x_1^6 - a - 1)}{(x_1^3 - 2a)^2(2x_1^6 + 2ax_1^3 + a + 1)^2} \times [4x_1^9 + 8ax_1^6 + 4(a^2 - a - 1)x_1^3 - a(a + 1)] . \quad (29)$$

In discussing the signs of these quantities, we shall thus be concerned with the signs of the quantities

$$\phi_1(x_1) \equiv 10x_1^9 + 14ax_1^6 + (4a^2 - 7a - 7)x_1^3 - 4a(a + 1) , \quad (30)$$

and

$$\phi_2(x_1) \equiv 4x_1^9 + 8ax_1^6 + 4(a^2 - a - 1)x_1^3 - a(a + 1) , \quad (31)$$

and we note for future reference that

$$\phi_1(x_1) = \phi_2(x_1) + 3(x_1^3 + a)(2x_1^6 - a - 1) . \quad (32)$$

We now consider the equilibria in their various possible locations.

4. *Case of two oblate spheroids.* We have seen that this can arise only when

$$a < 1 . \quad (33)$$

Let the equilibria E_1 and E_2 be given by x_1 and x_2 where

$$x_1 < x_2 < 1 .$$

Hence, from (17), it follows that

$$2x_1^6 < a + 1 < 2x_1^3 , \quad a + 1 < 2x_2^6 < 2x_2^3 . \quad (34)$$

To examine the equilibrium E_2 , we have only to replace x_1 by x_2 in the relevant formulae. From (23), therefore, the interchange having been made, it is evident that at E_2 , $\lambda_1 \lambda_2 < 0$, and the equilibrium is unstable. But at E_1 , $\lambda_1 \lambda_2 > 0$, and hence the necessary and sufficient condition for stability is that $\lambda_1 + \lambda_2 < 0$, and hence that $B > B_0$. If $x_1^3 < 2a$, then $B_0 < 0$ and necessarily $B > B_0$. But if $x_1^3 > 2a$, then $B_0 > 0$, and the equilibrium at E_1 is unstable unless $B > B_0$.

The condition $x_1^3 < 2a$ can be expressed in terms of a and A , if we refer to the curve

$$(\alpha + 1/2)^2 = 4(A - 47/16) , \quad \alpha \equiv 1/a , \quad (35)$$

which is the condition that $\phi(2a) \equiv \phi(2/\alpha) = 0$. This is evidently a parabola which opens upward, and is the third of the curves of the figure. It is tangent to the hyperbola at the point $(-1/2 + \sqrt{33}/2, 5)$, and it intersects the straight line at $(2, 9/2)$ and at $(3, 6)$. When the point (α, A) lies above the parabola, then $y_1 < 2a < y_2$. When the point lies between the parabola and the hyperbola, we have either $2a < y_1 < y_2$, or else $y_1 < y_2 < 2a$, according as $\phi'(2a)$ is negative or positive. But $\phi'(2a) = 2a(5 - A)$. Hence when $A < 5$ and the

point (α, A) lies between the two curves, then $y_1 < y_2 < 2a$, and when $A > 5$ and the point lies between the two curves, then $2a < y_1 < y_2$. Hence the equilibrium at E_1 is necessarily stable when the point (α, A) lies above the parabola, and also when the point lies below the line $A = 5$. In other cases, for points above $A = 5$, but below the parabola, the equilibrium is stable only when B exceeds the positive quantity B_0 .

When two non-spherical equilibria exist and in both states the cell is an oblate spheroid, a situation which can arise only when $1/\alpha \equiv a < 1$, then the spherical equilibrium is always stable, the more nearly spherical of the two non-spherical equilibria is necessarily unstable, and the other equilibrium is always stable provided the ratio x_1^3 of its polar to its equatorial radius is less than $2a$. The condition $x_1^3 < 2a$, when expressed in terms of a and A is that the point (α, A) shall lie either below $A = 5$ or else above the parabola (35). If $x_1^3 > 2a$, then the equilibrium at x_1 is stable only when B exceeds a certain positive quantity B_0 defined by (25). The parameters $\alpha \equiv 1/a$, A and B are all defined by (5) and the value of $y_1 = x_1^3$ at the equilibrium is the smaller of the two roots of (14).

We consider next the possible occurrence of periodic or quasi-periodic fluctuations about this equilibrium in case it is stable. If $x_1^3 > 2a$, and B has a value close to B_0 , then evidently $(\lambda_1 - \lambda_2)^2 < 0$ and the solution of the differential equations are quasi-periodic (and damped) in the neighborhood of the equilibrium. But if $x_1^3 < 2a$, then since $(\lambda_1 - \lambda_2)^2$ is certainly positive for B very small, it follows that values of B will exist such that quasi-periodicities occur only in case the numerator in (24) has a negative minimum for a positive value of B . This is equivalent to the statement that $f(C)$ in (27) has a negative minimum for a positive value of C . But the values of C and of f at this minimum are given by (28) and (29), so that $C_0 > 0$ if and only if $\phi_1(x_1) < 0$ while $f_{min} < 0$ if and only if $\phi_2(x_1) < 0$. But from (32) it follows that the second relation implies the first.

Consider, therefore, the inequality

$$4y_1^3 + 8ay_1^2 + 4(a^2 - a - 1)y_1 - a(a + 1) < 0, \quad (36)$$

where $y_1 = x_1^3$, with the assumption $y_1 < 2a$. We have seen that for this it is necessary that $a > 1/3$. For $y_1 = 2a$, the left member of (36) has the value $9a(8a^2 - a - 1)$. Consequently if $8a^2 - a - 1 < 0$, (36) is always satisfied for $y_1 < 2a$. But if $8a^2 - a - 1 > 0$, (36) will be satisfied only by values of y_1 , less than a certain value $y'_1 < 2a$. Hence the situation may be described as follows:

When two oblate spheroidal equilibria exist and $y_1 = x_1^3$ represents the smaller equilibrium ratio of polar to equatorial radius, then

whenever $8a^2 - a - 1 < 0$, there always exists a pair of numbers B_1 and B_2 such that when B satisfies $B_1 < B < B_2$ the equilibrium y_1 is stable and in the neighborhood of this equilibrium quasi-periodic fluctuations in y and in c occur as the cell approaches equilibrium. But if $8a^2 - a - 1 > 0$, such values B_1 and B_2 exist only in case y_1 is small enough to satisfy (36). When $8a^2 - a - 1 > 0$ and (36) fails, then whatever value B may have, the equilibrium will be stable and no fluctuations will occur.

5. *Case of two prolate spheroids.* We have seen that this can arise only when

$$a > 1 \quad (37)$$

Let the equilibria E_1 and E_2 be given by x_1 and x_2 where

$$1 < x_2 < x_1.$$

Hence it follows that

$$2x_1^3 < a + 1 < 2x_1^6, \quad 2x_2^3 < 2x_2^6 < a + 1. \quad (38)$$

Since $a > 1$ it follows that $4a > a + 1$, whence

$$x_1^3 < 2a. \quad (39)$$

To examine the equilibrium E_2 we replace x_1 by x_2 in the relevant formulae. From (23), therefore, it is evident that at E_2 , $\lambda_1 \lambda_2 < 0$ and the equilibrium is unstable. But at E_1 , $\lambda_1 \lambda_2 > 0$, and hence the necessary and sufficient condition for stability is that $\lambda_1 + \lambda_2 < 0$, and hence that $B > B_0$. It is evident from (25) that $B_0 > 0$, and from (24) that for $B = B_0$, $(\lambda_1 - \lambda_2)^2 < 0$. Therefore we can say

When two non-spherical equilibria exist and in both states the cell is a prolate spheroid, a situation which can arise only when $a > 1$, then the spherical equilibrium is necessarily stable, the more nearly spherical of the two non-spherical equilibria is necessarily unstable, and the other equilibrium is stable provided the parameter B exceeds a certain positive quantity B_0 . If B also exceeds a certain quantity $B_2 > B_0$, then a configuration in the neighborhood of this equilibrium approaches the equilibrium monotonically. But if $B_0 < B < B_2$, then the cell, when brought into the neighborhood of this equilibrium will approach the equilibrium through quasi-periodic oscillations about the equilibrium state. Criteria for these circumstances depend exclusively upon the combinations a , A , and B of the physical constants as defined in equations (5); the ratio $y_1 = x_1^3$ of the polar to the equatorial radius is defined by (14), of which it is the larger root, B_0 is defined by (25), and B_2 is the larger of the two values of B which cause the right member of (24) to vanish.

6. *Case of one oblate and one prolate spheroid.* Let the equi-

libria E_1 and E_2 be given by x_1 and x_2 where

$$x_1 < 1 < x_2 \quad (40)$$

so that, by this and (14) it follows that

$$2x_1^6 < 2x_1^3 < a + 1, \quad a + 1 < 2x_2^3 < 2x_2^6. \quad (41)$$

For discussing the equilibrium of the prolate spheroid, x_1 must be replaced by x_2 in the relevant formulae. From (23) and (41) it is evident that $\lambda_1 \lambda_2 > 0$ at both equilibria. Then (25) defines B_{01} corresponding to E_1 and corresponding to E_2 we may define

$$B_{02} = \frac{-(x_2^3 - 1)(x_2^3 - 2a)}{x_2(2x_2^6 + 2ax_2^3 + a + 1)}. \quad (42)$$

The equilibrium E_1 is stable provided $B > B_{01}$ and E_2 is stable provided $B > B_{02}$. We note that $B_{01} > 0$ when $x_1^3 > 2a$, and $B_{02} > 0$ when $x_2^3 < 2a$. Hence B_{01} and B_{02} cannot both be positive because of (40). From (14) we see that B_{01} and B_{02} are both negative and both equilibria are necessarily stable when the point (α, A) lies above the curve (35). If $\alpha < 2$ and (α, A) lies below (35), $B_{01} < 0$, $B_{02} > 0$, so that while the oblate spheroid is necessarily stable, the prolate spheroid may be unstable. If $\alpha > 3$ and (α, A) lies below (35), the prolate spheroid is necessarily stable but the oblate spheroid may be unstable.

Let there exist two non-spherical equilibria, one in which the cell is an oblate spheroid with the ratio $y_1 = x_1^3$, of polar to equatorial radii, and one in which the cell is a prolate spheroid with the ratio $y_2 = x_2^3$. These ratios are determined by the equation (14), in which the a and A are defined by (5). The spherical equilibrium is always unstable, whereas at least one of the non-spherical equilibria is bound to be stable: the equilibrium x_1 if the point (α, A) lies in the lower region between the curve (35) and the second of curves (15), the equilibrium x_2 if the point lies in the upper of these regions, and both if the point lies above both curves. In either of the first two cases, the other equilibrium is also stable provided B exceeds the positive one of the two quantities B_{01} as defined by (25) or B_{02} as defined by (42).

Consider finally the possibility of quasi-periodicities. If B_{01} is positive, the cell will approach the equilibrium state x_1 through quasi-periodic fluctuations, provided B is sufficiently close to B_{01} . If B_{02} is positive there will be a similar approach to x_2 provided B is sufficiently close to B_{02} .

Suppose $B_{01} < 0$. Periodicities exist for suitable values of B provided $f(C)$ as defined by (27) has a negative minimum for a positive value of C . But $B_{01} < 0$ only when $x_1^3 < 2a$, and hence for periodicities we must have $\phi_1(x_1) < 0$ and $\phi_2(x_1) < 0$, where ϕ_1 and ϕ_2 are

defined by (30) and (31) respectively. But, in view of (32) it appears that $\phi_2(x_1) < 0$ implies $\phi_1(x_1) < 0$. If $8a^2 - a - 1 < 0$, then $\phi_2(x_1) < 0$ for any $x_1^3 < 2a$, since $\phi_2 < 0$ when $x_1^3 = 2a$. If $8a^2 - a - 1 > 0$, then *a fortiori* $a > 1/3$, whence $4a > a + 1 > 2x_1^3$. When $x_1^3 = (a + 1)/2$, then $\phi_2(x_1) = 3(a + 1)(3a^2 - 1)/2$. Hence if $8a^2 - a - 1 > 0$ but $a < \sqrt{3}/3$, $\phi_2(x_1) < 0$ necessarily. But if $a > \sqrt{3}/3$ then there is a single positive $x_1^3 < (a + 1)/2 < 2a$ such that $\phi_2(x_1) = 0$, and if $x_1 < x_1'$, $\phi_2(x_1) < 0$.

In the case of a single oblate spheroid of equilibrium with x_1^3 the ratio of polar to equatorial radius, there is at most a finite range of values such that if B , as defined by (5), is on this range, there will be quasi-periodic fluctuations in the vicinity of the stable equilibrium. This range always exists unless $a > \sqrt{3}/3$, which implies that $x_1^3 < 2a$, and it will exist also in the latter case unless x_1 is such that $\phi_2(x_1) > 0$, where ϕ_2 is defined by (32).

At the equilibrium x_2 , if $B_{02} > 0$ a range of values of B always exists for which quasi-periodicities exist. We can have $B_{02} < 0$ only when $x_2^3 > 2a$, as appears from (42). Then the conditions for the existence of such a range are $\phi_1(x_2) > 0$ and $\phi_2(x_2) > 0$. But from (32) and (41) it appears that the second of these inequalities implies the first. If $8a^2 - a - 1 > 0$ then the second inequality is satisfied for any $x_2^3 > 2a$ since it is satisfied when $x_2^3 = 2a$. If $8a^2 - a - 1 < 0$, then there will exist an x_2' such that $x_2'^3 > 2a$, $\phi_2(x_2') = 0$, and when $x_2 > x_2'$ then such a range exists.

In the case of a single prolate spheroid of equilibrium with x_2^3 the ratio of polar to equatorial radius, there is at most a finite range of values such that if B , as defined by (5), is on this range, there will be quasi-periodic fluctuations about the stable equilibrium. This range always exists unless $8a^2 - a - 1 < 0$ and $x_2^3 > 2a$, and if this is true the additional condition $\phi_2(x_2) > 0$ must be satisfied in order for the range to exist.

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